REMARKS

Claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65 and 67-99 are pending in the application, of which claims 2, 3, 75 are being amended.

The claim amendments to claims 2 and 3 to recite that the "gel-to-liquid crystal transition temperature is greater than room temperature ..." is supported by the Specification at page 5, lines 3-7.

Claim 75, 80, 90 and 91 are being amended for cosmetic reasons.

Thus, the claim amendments are supported by the Specification and add no new matter, and consequently, should be entered.

Reconsideration of the present rejection is respectfully requested in view of the arguments presented herein and the Declaration of Dr. Jeffry Weers submitted herewith.

1. Double Patenting Rejection

The Examiner maintained the rejection of claims 1-3, 8-9, 11-15, 17-22, 27-32, 44-55, 59-62, 64-65, and 67-78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27-30, 34-37, 41-45 of copending Application No. 09/568,818.

As acknowledged by the Examiner, when either the present application or the 09/568,818 application is indicated as allowable, the double patenting issue will be suitably addressed in the other application.

2. Rejection Under 35 U.S.C. 112 of claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65 and 67-99

The Examiner rejected claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65 and 67-99 under 35 U.S.C. 112 as being indefinite for failing to particularly and distinctly claim the subject matter of the invention.

The Examiner continues to state that the limitation "sufficiently high to increase the..." renders the claim indefinite because it is not clear what amount of polyvalent ion is encompassed by the claim.

This rejection is respectfully traversed. The language of claim 1, for example, recites that the "molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation."

This language is not indefinite because the Specification teaches molar ratios which are suitable to increase the gel-to-liquid crystal transition temperature of the particles as claimed. Specifically, the instant disclosure teaches that:

> According to the invention, the polyvalent cation is present in an amount effective to increase the Tm of the phospholipid such that the particulate composition exhibits a Tm which is greater than its storage temperature Ts by at least 20°C, preferably at least 40°C. The molar ratio of polyvalent cation to phospholipid should be at least 0.05, preferably 0.05-2.0, and most preferably 0.25-1.0.

(Specification, page 8 lines 30 to 34.) Numerous examples are also given, namely Examples 1 to XVI, of different compositions of the claimed invention and its properties. Thus, the claimed invention is clearly supported by the disclosure and not indefinite.

Should the Examiner maintain this rejection, Applicant requests a further explanation of the Section 112 rejection to adequately respond.

3. Rejection Under 35 U.S.C. § 103(a) of Claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65 and 67-78

The Examiner rejected claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65 and 67-99, under 35 U.S.C. 103 (a), as unpatentable over Weers et al. (6,309,623) in view of Materne et al. (GB 2065659). The rejection is respectfully traversed.

The Weers at al. patent does not teach the claimed particulate composition for delivery to the pulmonary system, the composition comprising particles comprising an active agent, *a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation*, as recited in Claim 1.

Instead Weers at al. teaches that "in particularly embodiments, the structural matrix is associated with, or comprises, a surfactant such as, a phospholipid or fluorinated surfactant" and that "although not required, the incorporation of a compatible surfactant can improve the stability of the respirator dispersions, increase pulmonary deposition, and facilitate the preparation of the suspension." Thus, Weers at al. teaches the use of phospholipids as optional surfactant additions to improve the stability of respiratory dispersions of particles. (Column 15, line 62 to about 16 line 2.) Weers at al. further teaches that such lipid surfactants should have particular gel to liquid crystal phase transition temperatures;

> "Lipids, including phospholipids, from both natural and synthetic sources are particularly compatible with the present invention and may be used in varying concentrations to form the structural matrix. Generally, compatible lipids comprise those that have a gel to liquid crystal phase transition greater than about 40° C.

(Column 16, lines 44-49). Thus, Weers et al. teaches the optional use of surfactant lipids to improve the stability of respiratory dispersions of particles, and also teaches that such lipid surfactants should that have a gel to liquid crystal phase transition temperature of greater than about 40°C.

The difference between the teachings of the Weers et al. patent and the instant Specification is explained by the first named inventor of the Weers et al. patent, Dr. Jeffry G. Weers, in paragraphs 9-16 of the attached Declaration (Weers Declaration).

In teaching that the problem of compatibility of the lipid addition to the other particle constituents is easily solved by selecting a lipid which has particular minimum gel to liquid crystal phase transition temperature; Weers et al. teaches against the much more complex solution of chemically altering a phospholipid to obtain a higher Tm. Also, nowhere does Weers et al. teach or suggest that a phospholipid can be chemically modified by a polyvalent cation to have a gel to liquid crystal phase transition temperature that is higher than that of the unmodified phospholipid, as claimed. Clearly, one of ordinary skill in the art would not have the motivation to devise the more difficult solution of increasing a gel to liquid transition temperature of a particular phospholipid by chemical modification of its structure, when it is taught by Weers et al. that any compatibility problem is easily solved simply by selection of an appropriate phospholipid from those that are readily commercially available.

The Examiner acknowledges that Weers et al. lacks an exemplification of a composition comprising saturated phospholipid and divalent cation, and a teaching of the ratio of cation to phospholipid. However, Weers et al. simply does not teach or suggest use of a polyvalent ion in the claimed minimum molar ratios to achieve the surprising result of changing its phase transition temperature. Instead, as acknowledged by the Examiner, Weers et al. teaches that optionally, various materials including inorganic salts such as calcium chloride can be added to, for example, adjust the pH of the feedstock. Weers et al. does not suggest that a polyvalent ion can be

used to increase Tm of a phospholipid and does not mention why such a combination is desirable or the molar ratio recited in the present claim. There is simply no motivation suggested or taught by Weers et al. to derive the particles of claim 1.

The Examiner continues to suggest that Materne et al. teaches calcium phosphatidycholine for pharmaceutical preparations, and also teaches a molar ratio of cation to phospholipid of 0.5:1 to 2:1. The Examiner further states that such a ratio is taught as highly stable for pharmaceutical formulation.

However, Materne et al. teaches the addition of calcium chloride to an unsaturated phospholipid, and not a saturated phospholipid, as explained in paragraphs 17-19 of the Weers Declaration. Materne et al. teaches phosphatidylcholines which are plastic materials of low stability, and difficult to process and handle. This description of physiochemical properties and appearance corresponds to phosphatidylcholines that are unsaturated with particles that often fuse into large conglomerates due to temperature or moisture induced aggregation. (Para 17, Weers Declaration.) In contrast, saturated phosphatidylcholines arrive from vendors as flowable powders which are typically chemically stable because they contain no double bonds that can be oxidized; thus, these materials are not difficult to handle under ambient conditions. Materne et al. further describes the phosphatidylcholines as being yellow in color - which is also indicative of oxidation processes involving double bonds present in unsaturated materials. In contrast, saturated phosphatidylcholines are generally white in appearance. (Paragraphs 18-19, Weers Declaration.)

Thus, Materne et al. clearly teaches the use of unsaturated phospholipids and not saturated phospholipids. Materne et al. provides no motivation for substituting a saturated phospholipid for the described unsaturated phospholipid. Thus, Materne et al. does not cure the deficiencies of Weers et al. Accordingly, there would have been no motivation to substitute the unsaturated phospholipids taught by Materne et al. with the claimed saturated phospholipids.

Furthermore, even if a prima facei case of obviousness is established by the Examiner, the surprising and unexpected results of the claimed invention refute the obviousness rejection. The instant claims are to particles comprising saturated phospholipids in combination with a polyvalent cation in a molar ration that increases the gel to liquid transition temperature of the particles. As explained by Dr. Weers, the addition of calcium chloride to a saturated phospholipid as claimed, provides an unexpected increase in gel to liquid crystal transition temperature. (Paragraphs 6-8, Weers Declaration.) The inventive aspect of particles comprising a saturated phospholipid in combination with a polyvalent cation in a particular molar ratio to provide a higher gel to liquid transition temperature is an unexpected result negating the rejection of obviousness.

Thus, the cited combination of Weers et al. and Materne et al. simply does not sustain a prima facie obviousness rejection of claim 1, which recites a saturated phospholipid, a polyvalent cation, and a molar ratio of the two compounds that is higher than 0.5 to increase the gel to liquid transition temperature of the phospholipid containing particle. For these reasons, claim 1 and its dependent claims are patentable over Weers et al. and Materne et al.

Independent claims 31, 32, 44 and 59, all of which recite the molar ratio of polyvalent cation to saturated phospholipid 1 of at least 0.05 are also not rendered unpatentable by Weers et al. and Materne et al. for the same reasons. Claims 45-52, 55, 57, 58, 60-62, 64, 65, 67-71 and 73-78 also depend from one of claims 31, 32, 44 and 59, and are also allowable over Weers et al. and Materne et al.

Claims 72-78 are also patentable for the same reasons as claim 1, namely that the cited references do not teach a molar ratio of polyvalent cation to saturated phospholipid 1 of at least 0.05. In addition, Weers et al. and Materne et al. do not teach a particulate composition comprising a saturated, zwitterionic phospholipid as taught in claims 72-74, 77, and 78, nor do the cited references teach hollow particles as claimed in claim 76. For these reasons, claims 72-78 are independently allowable over the cited

references.

Claim 79, and the claims dependent therefrom, are also patentable over the cited references because the cited references do not teach a particulate composition for delivery to the pulmonary system, the composition comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation.

Claim 90, and the claims dependent therefrom, are also patentable over the cited references because the references do not teach a method of making a temperature stable particulate composition for delivery to the pulmonary system, the method comprising (a) forming a feedstock comprising a saturated phospholipid emulsion and an active agent; (b) adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2; and (c) drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage temperature of the porous particles by at least about 20° C.

CONCLUSION

The above-discussed amendments are believed to place the present application in condition for allowance. Should the Examiner have any questions regarding the above remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES, P.C.

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